

**REMARKS**

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

**Entry of Amendments**

By the foregoing amendment, the specification has been amended to delete reference to imbedded hyperlinks and to insert brief descriptions of drawings 1A, 1B, etc. The claims have been amended to delete non-elected claims. No new matter has been added by these amendments.

The pending claims are 17-23.

**Election/Restriction**

Applicants acknowledge that the restriction requirement has been made final. Although Applicants do not necessarily agree with the position taken in the Office Action, Applicants hereby cancel non-elected claims 1-16, without prejudice, in the interest of compact prosecution only.

**Priority**

Applicants hereby affirm their claim for priority.

**Drawings**

By the foregoing amendment, the specification has been amended to insert separate description of figures 1A-1E. Applicants submit that this is sufficient to overcome the objection in the Office Action.

Rejection under 35 USC § 112, First Paragraph

Claims 17-23 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicants respectfully traverse this rejection as follows.

The claims cover a method of predicting MSI status of a tumor. The method is practiced by determining in the tumor the number of adenosine nucleotides in a poly(A) tract of a RIZ nucleic acid molecule in the tumor. An abnormal number of adenosine nucleotides in the RIZ poly(A) tract indicates that the tumor is MSI-positive. Applicants have discovered and adequately disclosed within the instant specification that abnormal numbers of adenosine residues within a poly(A) tract of RIZ in a tumor is predictive of MSI(+) status. Such information is useful to clinicians, *inter alia* because MSI status correlates with efficacy of certain therapies and clinical outcomes.

The specification teaches that there are two major genetic instability pathways that have been recognized in cancers, one of which is microsatellite instability (MSI). *Specification*, page 2. Microsatellite instability results from defects in cells' DNA mismatch repair system. *Specification* page 3. Loss of mismatch repair enhances the process of mutagenesis and selection that underlies the development of cancer. *Id.* The mechanism of tumorigenesis of MSI(+) tumors is thought to involve frameshift mutations of microsatellite repeats within coding regions of affected target genes whose inactivation directly contributes to tumor development. *Id.* Frameshift mutations in poly-adenosine tracts of the RIZ gene were detected in a high percentage of MSI(+) tumor cells and cell lines, including tumors and cell lines derived from colon, gastric and endometrial tissues. *Specification*, pages 17-

18. In contrast, RIZ poly(A)-tract mutations were not detected in MSI(-) tumor cells and cell lines. *Id.* at 18. Accordingly, the determination that a tumor contains a RIZ poly(A) tract frameshift mutation strongly predicts that the tumor is MSI(+). *Id.*

The specification also sets forth two detailed examples demonstrating the high degree of correlation between mutation of poly(A) tracts of the RIZ gene and MSI(+) status of the cell lines. In Example 1, 22 MSI(-) and 24 MSI(+) tumor cell lines were tested. While a finite percentage of MSI(+) cell lines were positive for poly(A) tract mutations, none of the 23 tested MSI(-) sporadic colorectal cancers contained mutations in either of the poly(A) tracts, indicating that these regions are mutational hotspots in MSI(+) tumors only. *Specification*, page 25. In example 2, 179 primary gastrointestinal and endometrial tumors from patients undergoing surgery were analyzed. A finite percentage of MSI(+) gastric carcinomas, endometrial cancers, colorectal cancers and MSI(+) cell lines contained poly(A) tract mutations in the RIZ gene. In contrast, no RIZ mutations were found in 70 MSI(-) gastric carcinomas, indicating that these mutations are specific for MSI(+) tumors.

The question of adequacy of disclosure in the context of § 112, first paragraph, is whether the person of skill in the art could have practiced the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 735, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The key word is “undue,” not “experimentation,” as the law permits a fairly large amount of experimentation so long as it is not “undue”. *Id.* The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. *Id.* The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable

amount of guidance with respect to the direction in which the experimentation should proceed. *Id.*

Applicants submit that, applying the reasonableness standard set forth in *Wands*, the Office Action fails to establish that the claims as drafted are so broad compared to the detailed teaching of the specification as to be unpatentable. Following the teaching of the specification, the person of skill in the art could practice the invention with no more than routine experimentation. In order to predict the MSI status of a tumor, the person of skill in the art would need only determine the number of adenosine (A) nucleotides in a poly(A) tract of a RIZ nucleic acid molecule in said tumor. According to the detailed teaching of the instant specification, an abnormal number of adenosine nucleotides in the poly(A) tract of RIZ indicates to the person of skill in the art that the tumor is predicted to be MSI(+).

The Office Action does not allege that the person of skill in the art would not know how to determine the number of adenosine nucleotides in a poly(A) tract of RIZ nucleic acid. Nor would it be credible to do so, as sequencing of nucleic acids is routine for one of skill in the art. Rather, in its lengthy dissertation on the so-called *Wands* factors, the Office Action attacks the breadth of the terms “tumor,” “poly(A) tract” and “RIZ”.

According to the Office Action, a high degree of experimentation would be required to predict the MSI(+) status of every tumor type. The thrust of this argument seems to be that there are two different types of cells – those that are MSI(+) and those that are MSI(-), that one of skill in the art would not be able to predict *a priori* whether a particular cell is one or the other, and that it would thus require undue experimentation to determine whether each and every tumor type is MSI(+) or MSI(-).

Applicants submit that this line of reasoning misses the point of the invention, which is to “predict” the MSI status of a cell. The Office Action does not allege, nor would it be credible to do so, that the person of skill in the art – high skill, as admitted in the Office Action – would not be able to acquire a tumor sample, determine the number of adenosine nucleotides in a RIZ poly(A) tract, and ascertain whether that number was normal. An abnormal number of adenosine nucleotides is predictive of MSI(+) status. There is simply nothing required of the person of ordinary skill in the art to practice the claimed invention that is not taught in sufficient detail in the instant specification.

The Office Action makes much of the fact that many tumor types and cell lines are MSI(-). However, the fact that MSI is absent in a large number of cell lines and tumor types is not relevant to determining whether the person of skill in this particular art would be able to carry out the full scope of the claimed invention. What is important is whether that skilled person could determine the number of adenosine nucleotides in a poly(A) tract of RIZ nucleotide: a rather mundane, routine task for the skilled person in this art. True, a large number of cell lines might be tested and prove to have normal numbers of adenosine nucleotides in their poly(A) tracts; these would be predicted to be MSI(-). Likewise, a relatively small number of cells may be tested and shown to have abnormal numbers of adenosine nucleotides in their poly(A) tracts: these would be predicted to be MSI(+). As stated by the *Wands* court: “Enablement is not precluded by the necessity for some experimentation such as routine screening”. 8 USPQ2d at 1404. As routine screening is all that is required to predict the MSI status of any tumor according to the claimed method, it is unreasonable to hold that the claims are not enabled by the specification.

As mentioned above, the Office Action takes issue with the breadth of the terms “RIZ” and “poly(A) tract.” Applicants submit that the focus here, as above, should be on method steps – i.e. determining the number of adenosine nucleotides in the RIZ nucleic acid. Again, Applicants point out that there is nothing in the Office Action that even suggests that it would not have been within the skill of the ordinary practitioner in this art to measure the number of adenosine residues in a RIZ nucleic acid. That there are different RIZ nucleic acids (DNA, pre-mRNA, mRNA, etc.) and more than two poly(A) tracts within each RIZ nucleic acid are immaterial. The focus should be on what the person of ordinary skill in the art would have to do to practice the invention. It would have been a matter of routine for the person of skill in the art to determine the number of adenosine nucleic acids in a RIZ nucleic acid of any tumor. The Office Action fails to establish otherwise.

In fact, the analysis of the *Wands* factors outlined in the Office Action do not require the conclusion that a person of skill in the art would have to undertake undue experimentation to practice the invention as claimed. On the contrary, the factors point to the routine nature of the work necessary for the person skilled in the art to practice the invention. The references cited by the Office Action, as well as the instant specification itself, demonstrate that it is possible to predict the MSI status of a large number of tumors by applying the method steps recited in the instant claims.

In view of the foregoing remarks, Applicants submit that Office Action fails to make out a *prima facie* case of nonenablement. The person skilled in the art would clearly know how to determine the number of adenosine nucleotides in a poly(A) tract of a RIZ nucleic acid. Following the un rebutted evidence of the specification, an abnormal number of adenosine nucleotides in a poly(A) tract predicts an MSI status of MSI(+). Thus,

Applicants request that the rejection of claims 17-23 under 35 U.S.C. § 112, first paragraph, be withdrawn.

The § 102(a) Rejections

Claims 17-19 and 21-23 were rejected under 35 U.S.C. § 102(a) as being anticipated by Chadwick (PNAS, Vol. 97, No. 6, pages 2662-2667, March 2000) (“Chadwick”).

Applicants traverse this rejection.

The Office Action noted that the authorship of Chadwick is different from the inventorship (Huang and Chadwick) of the instant invention. The Office Action further noted that the rejection could be overcome by a duly executed *Katz* declaration. Applicants submit herewith a declaration under 37 C.F.R. § 1.132, in which inventors Shi Huang and Robert B. Chadwick declare that they are the sole inventors of the subject matter claimed in the instant application and that their co-authors on the Chadwick publication did not contribute to the conception of the subject matter disclosed in the Chadwick publication and claimed in the instant application. (See Exhibits A and B). Applicants submit that this declaration is sufficient to obviate the rejection over Chadwick. Withdrawal of the § 102(a) rejection over Chadwick is therefore requested.

Claims 17-19 and 21-23 were rejected under 35 U.S.C. § 102(a) as being anticipated by Piao et al. (Cancer Research, Vol. 60, No. 6, pages 4701-4704, September 2000) (“Piao”). Applicants traverse this rejection.

The Office Action noted that the authorship of Piao is different from the inventorship (Huang and Chadwick) of the instant invention. While the Office Action did not further note that the rejection could be overcome by a duly executed *Katz* declaration, Applicants submit herewith a declaration under 37 C.F.R. § 1.132, in which inventors Shi Huang and

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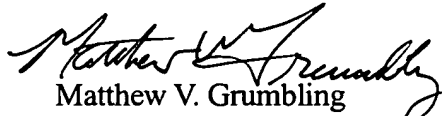
Robert B. Chadwick declare that they are the sole inventors of the subject matter claimed in the instant application and that Robert B. Chadwick's co-authors on the Piao publication did not contribute to the conception of the subject matter disclosed in the Piao publication and claimed in the instant application. (See Exhibits C and D). Applicants submit that this declaration is sufficient to obviate the rejection over Piao. Withdrawal of the § 102(a) rejection over Piao is therefore requested.

**CONCLUSION**

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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